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Zinc acetate lozenges may shorten common cold duration by up to 40% : [eLetter]

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Zinc acetate lozenges may shorten common cold duration by up to 40% [e-Letter]

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This is commentary to the following paper published in CMAJ:

Science M, Johnstone J, Roth DE, Guyatt G, Loeb M.

Zinc for the treatment of the common cold:

a systematic review and meta-analysis of randomized controlled trials.

CMAJ. 2012 Jul 10;184(10):E551-61.

<https://www.ncbi.nlm.nih.gov/pubmed/22566526>

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This commentary was published in May 28, 2012

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<https://www.cmaj.ca/content/184/10/E551/tab-e-letters#zinc-acetate-lozenges-may-shorten-common-cold-duration-by-up-to-40>

No replies to these comments were published by June 2021

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These comments were motivated by differences in the analysis and in the conclusions compared with the meta-analysis:

Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review.

Open Respir Med J 2011;5:51-8.

<https://www.ncbi.nlm.nih.gov/pubmed/21769305>

<https://doi.org/10.2174/1874306401105010051>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969>

See references available for this paper as links at:

<https://www.mv.helsinki.fi/home/hemila/Zn/TORMJ.htm>

See other papers on zinc lozenges and the common cold:

<https://www.mv.helsinki.fi/home/hemila/Zinc.htm>

Zinc acetate lozenges may shorten common cold duration by up to 40%

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The systematic review by Dr. Science et al. has a number of problems.

1. The meta-analysis suffers from a severe "apples and oranges" problem

Science et al. excluded the intranasal zinc trials from their review and that is acceptable. However, that does not mean that the authors should not read such studies. The intranasal zinc studies are relevant when considering the plausible biological mechanism of zinc on the common cold. Some intranasal zinc studies reported significant benefit against colds [1,2]. Patients should not be advised to use intranasal zinc, since there are cases of anosmia caused by such a therapy [3]; however, the reported benefits indicate that zinc administration may have local influence on the nose-throat region. In analogy, zinc lozenges (tablets intended to be dissolved slowly in the mouth) can influence the mouth-throat region locally, whereas zinc syrup, used by Kurugol [4,5], and ordinary zinc tablets do not have local effects on the mouth-throat region.

The explicit rationale for the zinc lozenge trials, starting from the Eby 1984 trial [6], has been that zinc may have local effects on the mouth-throat region. Therefore, lozenges have been composed so that they dissolve slowly and participants have been instructed to dissolve them slowly in the mouth [7-9]. If Science et al. have evidence that zinc lozenges do not have local effects, they should have presented such evidence to the readers. If they don't have such evidence, they should have separated the zinc lozenge studies (local effects on the mouth-throat region) from the zinc syrup studies [4,5] (systemic effects). The Kurugol trials are relevant to examine the effects of higher zinc intake levels, but they are not relevant to examine the local effects of zinc on the mouth-throat region. Authors of a systematic review should study the biology of the topic, so that they can understand which interventions should not be combined.

2. Subgroup analyses are not specific to the selected variables

In the Results section, Science et al. describe their Fig. 2 findings: "zinc reduced the duration of cold symptoms in adults but not in children". This comparison is based on 3 trials with children, but 2 of them were by Kurugol et al. [4,5]. The Kurugol trials: a) used zinc syrup which has no local effects on

the mouth-throat region [see Comment 1], b) used a low dose of zinc (30 mg/day), and c) were carried out in Turkey.

A basic principle in biostatistics is that, when two groups are compared on the basis of one variable, the groups should be very similar over all other relevant factors. This is the rationale for using randomization to divide participants in RCTs. In observational studies, the groups can be different in many ways but the differences are taken into account by statistical methods, so that the effect of the main variable is adjusted for confounding factors.

In Fig. 2, there is no basis to assume that the "adult subgroup" and the "children subgroup" are similar in all other ways except the age of the participants. In contrast, we know that the physiological location of the zinc effect (Kurugol used zinc syrup; all adult trials used zinc lozenges), the dose (Kurugol used 30 mg/day zinc; all adult trials used between 80 to 192 mg/day zinc), and the countries (Kurugol trial was carried out in Turkey; all adult trials were carried out in the western countries) substantially differ between the adult subgroup and the Kurugol trials of the children subgroup. Any of these three factors (or some further factors) could cause the differences between the adult and children groups in Fig. 2. The fact that Science et al. write that the subgroups "were defined a priori" has nothing to do with this problem.

Figs. 3 and 4 have the similar problems. For example, in Fig. 4, the Kurugol trials [4,5] are the only trials in the "zinc sulfate" group, yet the reader is misled to assume that the type of zinc salt is the only difference between 3 subgroups of Fig. 4. However, zinc sulfate was administered as syrup whereas zinc acetate and zinc gluconate were administered as lozenges. In addition, zinc sulfate was administered to children whereas zinc acetate was administered to adults, etc. Thus, there is no justification to state that the subgroup differences in Figs. 2 to 4 are specific to the selected 3 variables. The Abstract of the paper describes the subgroup differences without mentioning the severe biases in the subgroup comparisons.

3. The authors do not describe how they calculated the daily dose of zinc

In 2011, I published a meta-analysis of trials on zinc lozenges for the common cold and I used a pragmatic cut point of 75 mg/day for the low and high dosage of zinc [10]. This same limit, 75 mg/day, was used by Science et al. as described in their Methods. In my meta-analysis, I calculated that the dose of the Petrus trial was 89 mg/day, which was based on the Petrus et al. report: "The lozenges with zinc contained 9 mg of zinc" and the number of lozenges "averaged 9.9 lozenges per subject per day" [11]. However, in their Fig. 3, Science et al. list the Petrus trial under the "low-dose zinc" category meaning

that the dose was under 75 mg/day. Thus, there is discrepancy between the Methods and Fig. 3 of the Science et al. paper, and the Petrus report.

4. The effect on common cold duration should not be calculated on the absolute scale

In studies measuring dichotomous outcomes, risk ratio (RR) is a standard measure for comparing study groups. The purpose of using RR is to adjust for the baseline variability in the occurrence of disease. The same approach should be used with continuous outcomes. Although there is random variation in the duration of colds in the placebo groups, there are also biological reasons why colds sometimes last longer and sometimes shorter. For example, over 100 viruses falling to a dozen virus groups can cause common cold symptoms. The set of viruses depends on the particular place and time, and therefore we should expect that the average colds differ between trials. In addition, the operational definition of the common cold varies between trials, which also generates variation in the baseline duration of colds. Such baseline variability should be taken into account when analyzing the effect of a treatment on common cold duration.

As an example of the problem of the absolute scale, if a 6-day cold is shortened by 2 days, it is not equivalent to a 2-day cold being shortened by 2 days although both differences are equal in the absolute scale. Therefore, it is more reasonable to calculate the relative effect of zinc, so that a 6-day cold shortened by 2 days and a 2-day cold shortened by 0.66 days both correspond to an equivalent 33% reduction. Calculating the relative effect corresponds to the normalization of all control groups to an episode duration of one unit or 100%.

In the zinc acetate subgroup of Fig. 4, the duration of colds in the placebo group of the Petrus trial [11] was 5.1 days, whereas in the placebo groups of the Prasad trials, the cold durations were 8.1 days [12] and 7.1 days [13], which are substantially longer than in the Petrus trial. Science et al. calculated the zinc effects of these 3 trials on the absolute scale and found very high heterogeneity: $I^2 = 87\%$. However, large part of the heterogeneity is caused by their usage of the absolute scale. I pooled the same 3 zinc acetate trials using the relative scale and found a 42% (95%CI: 35% to 48%) reduction in common cold duration by zinc acetate lozenges [10]. In the relative scale, there is much less heterogeneity between the 3 zinc acetate trials, $I^2 = 43\%$, indicating that the relative scale more efficiently captures the effect of zinc acetate lozenges than the absolute scale. Therefore, the 42% decrease in the duration of colds [10] is a much better way to summarize the effect of zinc acetate lozenges than the 2.67 day decrease calculated by Science et al.

5. Pooling all adverse effects is unsound when there is strong evidence of heterogeneity

If the findings of several trials are homogeneous and the interventions are identical, then it may be sound to collect all reports of adverse effects and calculate pooled estimates. However, if the interventions are substantially different and there is very strong evidence of heterogeneity in the findings, there is no rationale for pooling the adverse effects over all trials.

Given that we can identify a subgroup of 3 trials where zinc is highly effective [11-13], the relevant question is adverse effects of zinc in these 3 trials. If some other formulations of zinc lozenges do not shorten colds, it is irrelevant to ask whether such ineffective lozenges cause adverse effects, because it does not make sense to use them anyway.

In their Fig. 6., Science et al. show the findings for adverse effects and pool them as if there might be universal same-size adverse effects of zinc irrespective of the composition of lozenges. Eby has pointed out that the adverse effects of zinc lozenges, such as bad taste, can be explained largely by the differences in the composition of the lozenges [7-9]. Therefore pooling adverse effects of all diverse lozenges is not sound. Furthermore, all the 3 zinc acetate trials which found the greatest benefits [11-13] are missing from Fig. 6.

In the most recent zinc acetate lozenge trial, with 92 mg/day zinc, Prasad et al. wrote: "The zinc and placebo groups did not differ significantly in the incidences of any of the adverse effects, including diarrhea, constipation, sweet taste, sour taste, bitter taste, aftertaste, dry mouth, mouth irritation, or bad taste. None of the subjects complained of either abdominal pain or vomiting" [13]. Thus, it seems possible to formulate effective zinc acetate lozenges that have minimal adverse effects. The fact that some other zinc lozenge formulas have caused adverse effects is no counterargument to the Prasad 2008 zinc lozenge formula [13]. Thus, Fig. 6 is irrelevant when considering whether zinc acetate lozenges [11-13] cause adverse effects or not.

6. A large number of minor problems

In addition to the major problems described above, there are numerous minor problems in the paper, but I will point out only a few examples.

Science et al.'s reference 17 is the early version of the Cochrane review on zinc for the common cold [14]. However, the early version was withdrawn 5 years ago [15] and has been replaced with a new version which was published in 2011 [16]. Why do Science et al. refer to a withdrawn paper?

In their Methods section, Science et al. writes: "We included studies if they were randomized controlled trials". In Table 1, they list 17 studies, including the Weismann trial [17]. However, Weismann did not describe the method of allocation in their paper. Therefore, I contacted Dr. Weismann and he wrote to me that their study used alternative allocation (email 2 July, 2010 [10]). Thus, Science et al. state that randomization was an inclusion criterion, yet they include a study that was not randomized.

In their Figs. 2 to 4, Science et al. give the Petrus trial results as 3.8 (SD 1.4) days in the zinc lozenge group and 5.1 (SD 2.8) days in the placebo group. In the original report, Petrus et al. gave the accuracy of the mean as SE (standard error) and they did not report the SD [11]. Since the SE was very inaccurately reported, I contacted the statistician of the Petrus group and got their accurate results: 3.797 (SD 1.630) days in the zinc group and 5.106 (SD 2.955) days in the placebo group (Ken Lawson, email 4 Mar 2009 [10]).

Science et al. write that "Study authors were contacted for information when required." This was not done for the Petrus [11] and the Weismann [17] trials although their reports clearly required further information.

Science et al. write: "Most of the trials did not provide adequate information on allocation concealment. All of the trials reported blinding of patients and health care professionals with placebos identical in appearance or with no identifying features." This statement indicates that the authors do not understand what "allocation concealment" means. The term "double-blind" (=blinding of patients and health care professionals) means that both the patients and researchers are unaware of the type of treatment until the trial is concluded. Therefore, neither of them can know to which group a patient had been allocated. Thus, reporting that a trial was "double-blind" means that there must have been allocation concealment irrespective of whether the authors use the term or not. Otherwise the patients and researchers could not remain blind until the conclusion of the trial. Therefore, Table 2 misleads the reader about the allocation concealment in many of the 17 studies.

In the Background section, Science et al. motivate their study by stating that the Cochrane review [16] did not carry out subgroup analysis. The Background states that variability among studies might be due to differences in zinc "dose and formulation". My 2011 paper [10] specifically analyzed these two issues and found that they gave explanations for much of the heterogeneity over 13 analyzed trials. Yet, those findings were ignored by Science et al. so that the Background gives a biased view on the previous research on the topic.

7. Science et al. conclude: "Until further evidence becomes available, there is only a weak

rationale for physicians to recommend zinc for the treatment of the common cold. The questionable benefits must be balanced against the potential adverse effects."

In 2011, I analyzed 13 zinc lozenge trials and divided them into 3 subgroups on the basis of the total daily dose of zinc and the type of the lozenge [10]. The results of all 13 studies were highly heterogeneous ($I^2 = 89\%$), but the zinc dose and formulation explained a large part of the heterogeneity. None of 5 trials with the lowest doses of zinc found benefit of the zinc lozenges and these 5 trials were not heterogeneous ($I^2 = 30\%$), suggesting that their negative findings may be explained by the low dose.

In the high-dose trials, great benefit was seen in 3 trials with zinc acetate and a smaller benefit was seen in 5 non-acetate trials. The group of 3 zinc acetate studies was not heterogeneous ($I^2 = 43\%$). In this group of 3 zinc acetate trials, colds were, on average, 42% shorter in the zinc lozenge groups compared with the placebo groups [10]. I do not understand why Science et al. claim that a 42% reduction in common cold duration by zinc acetate lozenges is "questionable."

The group of 5 trials with high-dose zinc salts other than acetate was heterogeneous ($I^2 = 84\%$). In this group of 5 trials, colds were, on average, 20% shorter in the zinc lozenge groups compared with the placebo groups. Exclusion of 2 trials which were methodologically least satisfactory led to, on average, 22% shorter colds in the remaining 3 trials with zinc salts other than acetate [10]. Thus, this subgroup indicates that zinc salts other than acetate can also shorten the duration of colds if the dose is high. However, the substantially greater benefit in the 3 zinc acetate trials indicates that further research should focus on zinc acetate lozenges.

If we compare my 2011 subgroup analysis [10] with that of Science et al., we can see that their subgroup analyses do not provide any explanations for the heterogeneity. With all their 8 trials together, the heterogeneity is very high with $I^2 = 95\%$. In 7 subgroups of Figs. 2 to 4, the I^2 within the subgroups varies between 78% and 92%, so that none of the 7 subgroups gives an I^2 below 50%. Thus, none of Science et al.'s subgroups is interesting if the goal is to find subgroups that are statistically homogeneous. Compare these I^2 levels with the 2 subgroups identified in my 2011 study [10] with I^2 levels of 30% and 43%, see above. Because Science et al. are using the absolute scale for measuring the common cold duration, even their analysis of the 3 zinc acetate trials [11-13] gives a high level of

heterogeneity ($I^2 = 87\%$), whereas my meta-analysis of the same 3 trials found a low level of heterogeneity ($I^2 = 43\%$)[see Comment 4].

The conclusion of my paper was that further research should focus on zinc acetate lozenges providing about 80 mg/day of zinc [10]. This is a very different conclusion compared with Science et al.'s conclusion: "large high-quality trials are needed before definitive recommendations for clinical practice can be made". A research oriented reader cannot know which kinds of zinc products should be tested in the future trials on the basis of such a conclusion.

The major question in the future trials is not their size, but the type of lozenges that are being tested. All the 3 zinc acetate lozenge trials were small (101 participants or less) [11-13], yet the size of the zinc effect was so great that each of the 3 trials was large enough to individually refute the null hypothesis. The main focus in the future trials should be on considering the best kinds of lozenges, and not on recruiting large numbers of participants for testing some poorly formulated zinc lozenges. Even though we need further research to find out what the optimal lozenge compositions and treatment strategies are, the great benefit and the minimal adverse effects in the zinc acetate trials [11-13] gives a strong rationale for physicians to suggest common cold patients to test zinc acetate lozenges (about 80 mg/day of zinc [10]).

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An update of this Cochrane review was retracted in 2015:
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